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Kempf, Werner ; Kazakov, Dmitry V ; Scheidegger, Paul E ; Schlaak, Max ; Tantcheva-Poór, Iliana

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Two Cases of Primary Cutaneous Lymphoma With a γ/δ+ Phenotype and an Indolent Course: Further Evidence of Heterogeneity of Cutaneous γ/δ+ T-Cell Lymphomas

Werner Kempf, MD, Dmitry V. Kazakov, MD, PhD,† Paul E. Scheidegger, MD,‡ Max Schlaak, MD,§ and Iliana Tantcheva-Poor, MD§*

Abstract: Cutaneous γ/δ+ T-cell lymphoma (CGD-TCL) is a rare but aggressive lymphoma associated with a poor prognosis in most patients. The clinicopathological spectrum is variable including predominantly epidermotropic infiltrates manifesting with patches and plaques or tumors with dermal and/or subcutaneous infiltrates. The diagnosis of CGD-TCL requires the demonstration of a γ/δ+ phenotype by immunohistochemistry. We report 2 patients with epidermotropic cutaneous T-cell lymphomas displaying a γ/δ+ phenotype, but exhibiting an indolent course. In one patient, the clinical presentation was similar to mycosis fungoides in patch and plaque stage, but recurrent blister formation within the lesions was observed accompanied by fever and arthralgias, whereas the second patient presented with 2 localized erosive plaques on the left temple and dense epidermotropic and dermal diffuse and folliculotropic infiltrates of atypical small-to-medium–sized lymphocytes. These cases corroborate the view that expression of a γ/δ+ phenotype in cutaneous T-cell lymphomas per se does not portend a worse prognosis and that CGD-TCL may represent a clinically and prognostically heterogeneous group.

Key Words: cutaneous lymphoma, aggressive, gamma-delta lymphoma, cytotoxic, mycosis fungoides, PD-1

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INTRODUCTION

The γ/δ T cells are a minor subset (<5%) of peripheral blood lymphocytes, representing an essential part of innate immune system and playing an important role in immunosurveillance.[1] By definition, they express the γ/δ T-cell receptor (TCR) and cytotoxic molecules. When activated, γ/δ T cells can additionally express one or more natural killer–associated surface molecules (CD56, CD16, CD57), morphologically appearing in the activated stage as large and granular cells. The γ/δ+ T cells are only exceptionally encountered in cutaneous inflammatory lymphocytic infiltrates, and usually their number does not exceed 5%–10% of the entire infiltrate.[2] Their malignant counterparts are thought to derive from local populations residing in some epithelial tissues, mirroring distribution of γ/δ+ T-cell lymphomas, namely the skin and intestine.

Cutaneous γ/δ+ T-cell lymphoma (CGD-TCL) is a rare and usually aggressive disease with a poor prognosis.[3–5] It is listed as a provisional entity in the World Health Organization (WHO)–European Organization for Research and Treatment of Cancer (EORTC) classification and represents a distinct lymphoma entity in the WHO classification (fourth edition, 2008).[4,6] Histologically, CGD-TCL presents with epidermotropic, dermal and/or subcutaneous infiltrates, or combinations of these patterns even in the same individual. In the past, the lack of α/β TCR expression (beta F1) by neoplastic lymphocytes was uniformly accepted as a criterion for assigning a γ/δ TCR phenotype, but recently, a new commercially available antibody recognizing the TCRγ subunit of the TCR in formalin-fixed and paraffin-embedded tissue was introduced.[7] Using this antibody, 2 groups have recently conducted studies on a large series of cutaneous T-cell lymphoma (CTCL) and concluded that the expression TCRγ is not exclusive to CGD-TCL because TCRγ was also identified in rare cases of other CTCL such as mycosis fungoides (MF) and lymphomatoid papulosis (LyP).[8,9] We present 2 cases of primary CTCL with expression of TCRγ, but an indolent course supporting the suggestion that CTCL with a γ/δ+ phenotype may represent a prognostically heterogeneous group and may clinically and histologically overlap with MF.[8,10]

CASE 1

Clinical Features

A 64-year-old man presented with asymptomatic, generalized, symmetrical, partly confluent patches and indurated plaques involving the trunk, upper and lower extremities, inguinal areas, and anterior neck that had been present for about a year. Some of the red-brown lesions were scaly, whereas others were circinate (Figs. 1A–C). No symptoms were reported, but the patient stated that he had been experiencing episodes of high fever (up to 38–39°C), arthralgia (hands and wrists), and vesicles and blisters (Fig. 1D) occurring approximately once per month and lasting for 2–3 days during the previous year. Blisters always healed leaving no scars. The clinical diagnosis was bullous lupus erythematosus or erythema gyratum repens. All laboratory results including peripheral blood lymphocyte count, viral serology (herpes simplex virus 1/herpes simplex virus 2, HIV, and human herpesvirus 8), and hepatitis serology (Hepatitis B surface antigen,

From the *Kempf Und Pfaltz Histologische Diagnostik, Zürich, Switzerland; †Department of Pathology, Faculty of Medicine in Pilsen, Charles University in Prague, Prague, Czech Republic; ‡Dermatology Practice, Brugg, Switzerland; and §Department of Dermatology, University of Cologne, Cologne, Germany.

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Reprints: Werner Kempf, MD, Kempf und Pfaltz Histologische Diagnostik, Seminarstrasse 1, CH-8042 Zürich, Switzerland (e-mail: werner.kempf@access.uzh.ch).

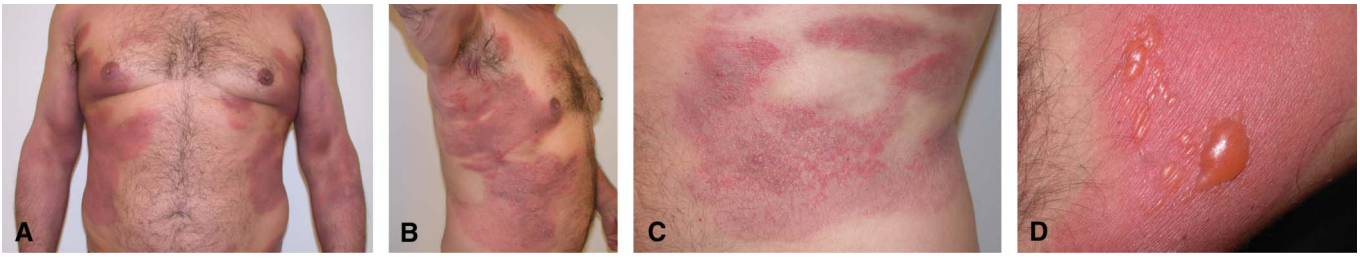

FIGURE 1. Case 1. A and B, Widespread symmetrical patches involving the trunk and extremities. C, Close-up of some lesions. D, Blister formation within a plaque on left upper arm.

anti–hepatitis C virus antibodies) were normal/negative. The patient's family history was significant for multiple malignant tumors including pulmonary carcinoma (father), Hodgkin disease (older brother), and brain tumor (youngest brother).

After histological diagnosis of epidermotropic cutaneous lymphoma, the patient underwent staging investigations including bone marrow biopsy and positron emission tomography/computed tomography, but no extracutaneous disease was found. Methotrexate in combination with psoralen-UV-A was administered but resulted in no improvement, though episodes of fever and blisters become less frequent. Acitretin 2 × 10 mg was then tried but that was also ineffective. Prednisone (first 50 mg, later 15 mg/d) was administered in combination with topical steroids (betametasone-17-valerate) cream. Most skin lesions (above 75%) regressed, and the patient is alive with few patches on the extremities, 19 months after diagnosis (Fig. 2).

Histopathological, Immunohistochemical, and Molecular Biologic Data

Four biopsies taken within a year and one specimen for direct immunofluorescence (DIF) studies were available for review. All 4 biopsies showed similar features (only density of the infiltrate varied), including scale, crusts, spongiosis, and an infiltrate composed of small lymphocytes with only slightly convoluted nuclei infiltrating the epidermis, focally lining up in the basal layer. Rare intraepidermal lymphocytes were larger than their dermal counterparts (Figs. 3A, B). Occasional neutrophils, eosinophils, and macrophages were present, the latter in foci with subtle vacuolar alteration at the dermoepidermal junction. One of the 4 biopsies showed subepidermal and subsequent intraepidermal blisters and an admixture of eosinophils in addition to the above-described epidermotropic infiltrates but no apoptotic keratinocytes in the detached epidermis (Fig. 3C).

Immunohistochemically, the infiltrate consisted exclusively of T cells expressing CD3 (80%–90%), CD4 (50%), and TCRγ (80%) (Fig. 4). Only occasional cells expressed CD2, CD7, and beta F1. No expression was seen with CD56 and CD57. T-cell intracellular antigen-1 was expressed by almost all γ/δ+ lymphocytic tumor cells, whereas granzyme B was absent. There were slight differences regarding expression of CD30 and PD-1 between the initial biopsy and the one taken 10 months later. Whereas in the initial specimen, approximately 20% of small lymphocytes (especially intraepidermal ones) expressed CD30 and PD-1, the number of CD30 and PD-1–positive cells amounted to 70%–80% in the subsequent biopsies including the one with blister formation.

DIF of the biopsy with blister formation revealed no deposits of immunoglobulin IgA, IgG, IgM, C3, or fibrinogen along the junctional zone or within the epidermis. Furthermore, indirect immunofluorescence and salt-split skin examination did not show antibodies against basement membrane components or epidermal antigens.

Molecular biologic studies using BIOMED 2 primers revealed monoclonal rearrangements of TCRγ genes.[11] Epstein-Barr virus–encoded small RNA (EBER) in situ hybridization was negative.

DIF examination revealed no abnormal deposits, arguing against a bullous disorder or lupus erythematosus.

FIGURE 2. Case 1. Posttreatment clinical appearance with regression of the lesions.

CASE 2

Clinical Features

An 82-year-old man presented with 2 rapidly growing lesions situated between the lateral canthus and the ear. Both lesions, one small and one large, were slightly elevated and crusted with an erythematous rim. A scar was evident above the larger lesion (Fig. 5A). No significant medical or family history was known.

After histological diagnosis, the patient underwent clinical investigation (except for bone marrow biopsy); no extracutaneous disease was identified. The patient was treated by local radiotherapy 2 × 4 Gy that resulted in complete remission (Fig. 5B). The patient is alive with no evidence of disease 11 months after diagnosis.

Histopathological, Immunohistochemical, and Molecular Biologic Data

The epidermis was focally ulcerated, but otherwise largely atrophic with loss of rete ridges. The dermis contained a dense diffuse infiltrate composed of small-to-medium–sized lymphocytes with irregular hyperchromatic nuclei. The cells displayed marked epidermotropism lining up on the basal layer of the epidermis and

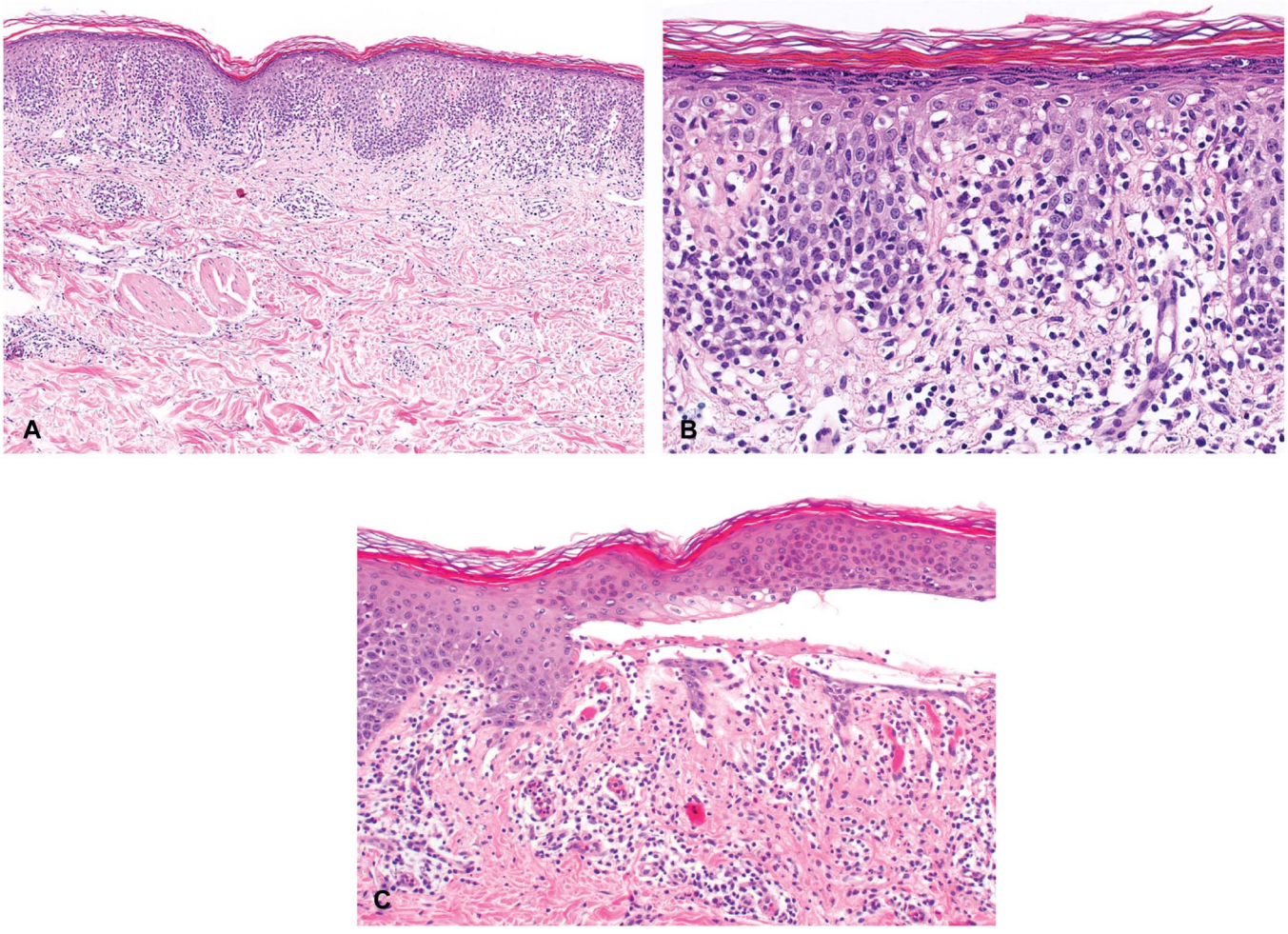

FIGURE 3. Case 1. A and B, Epidermotropic infiltrate composed of small lymphocytes showing striking epidermotropism with lining up in the basal layer of the epidermis. C, Subepidermal and intraepidermal blister formation.

also forming a small collection in the spinous layer (Pautrier microabscesses). In addition, there was marked folliculotropism, with virtually all vellus hair follicles present in the specimen being diffusely infiltrated by the lymphoid cells (Fig. 6).

Immunohistochemically, the infiltrate consisted exclusively of T cells expressing CD3 (100%) and TCRγ (70%) (Fig. 7). Other T-cell markers were expressed as follows: CD2 (10%), CD4 (20%), CD56 (weak, 10%), beta F1 (10%), and PD-1 (10%) (Fig. 7). Cytotoxic markers could not be examined because of the lack of sufficient tissue. Negative immunoreactivity was seen with CD7, CD20, and CD30. The proliferation index (MIB-1) of atypical cells was 70%.

Monoclonal rearrangements of TCRγ genes were detected using BIOMED 2 protocol.[11] EBV in situ hybridization (EBER) was negative.

DISCUSSION

We report 2 patients with epidermotropic lymphoid infiltrates in which the neoplastic cells expressed TCRγ as demonstrated by immunohistochemistry on formalin-fixed and paraffin-embedded tissue. Based on this finding, the diagnosis of CGD-TCL has to be seriously considered, particularly because CGD-TCL may histologically present with predominantly epidermotropic infiltrates.[6] CGD-TCL is generally regarded as an aggressive lymphoma with a poor prognosis. In our patients, however, the disease did not follow the expected aggressive course. In both the patients, the lymphoma was controlled by radiotherapy or steroids. In regard to this unusual indolent course and the clinical presentation in patient 1, MF with a γ/δ+ phenotype has to be considered as a differential diagnosis, especially because other CTCL recently have been found to express this phenotype rarely.[8,9] Only a few cases diagnosed as MF or MF-like lymphoma with a γ/δ+ phenotype have been reported.[12–14] Guitart et al[8] in their series of 53 cases of CTCL with γ/δ+ phenotype identified obviously 6 such patients to whom they referred as "MF-like" CGD-TCL; the disease in these patients followed a more indolent course. In contrast, some experts classified similar cases of epidermotropic infiltrates of TCRγ+ cells based on the clinical presentation with patches and plaques straightforward as MF, labeling them as "TCRγ+ MF."[9] In our patient, the patches and plaques were clinically typical for MF. The episodes of high fever and blisters are very unusual although blister formation

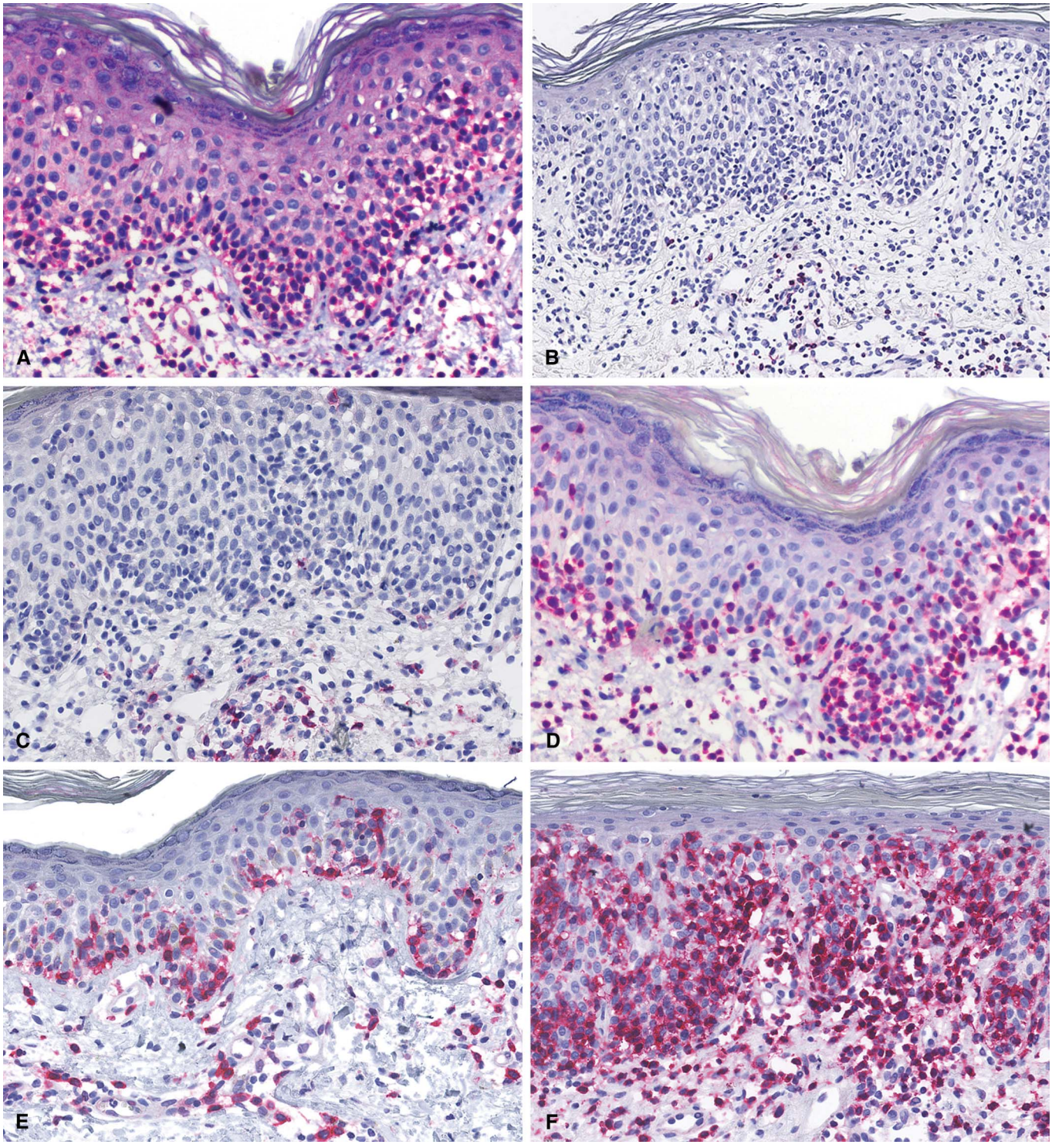

FIGURE 4. Case 1. Immunohistochemical staining for TCRγ (A); beta F1 (B); CD2 (C, note loss of CD2); CD3 (D); CD30 (E); and PD-1 (F).

has been documented in a patient with MF (so-called MF bullosa), whereas fever and symptoms of rheumatic diseases are not uncommonly observed in CGD-TCL.[15,16] The reason for recurrent blister formation is unknown. It can be speculated that cytokines released in a cyclic manner result in blister formation, fever, and arthralgias. Notably, the neoplastic cells in this case also expressed CD30, thus making LyP type D a histological differential diagnostic consideration.[17] However,

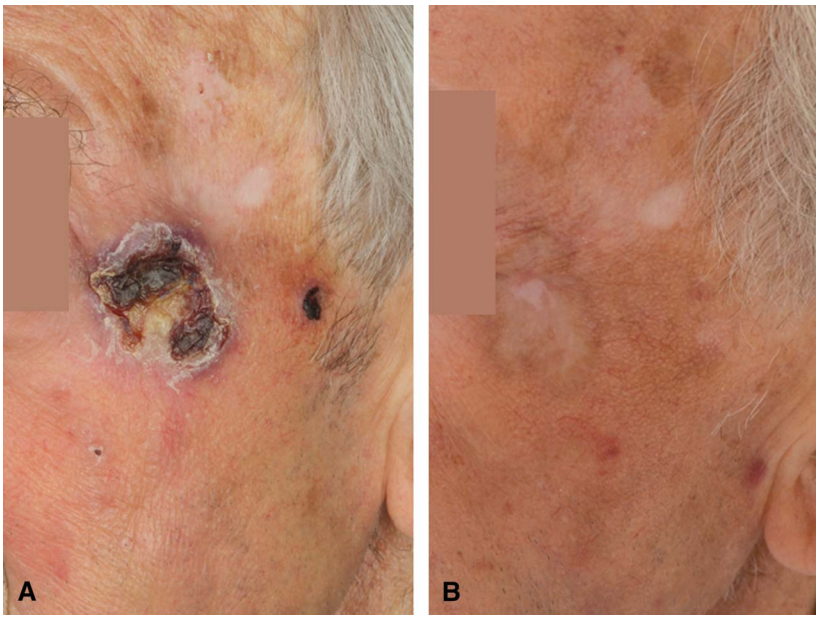

FIGURE 5. Case 2. The clinical appearance of the lesions before (A) and after (B) treatment.

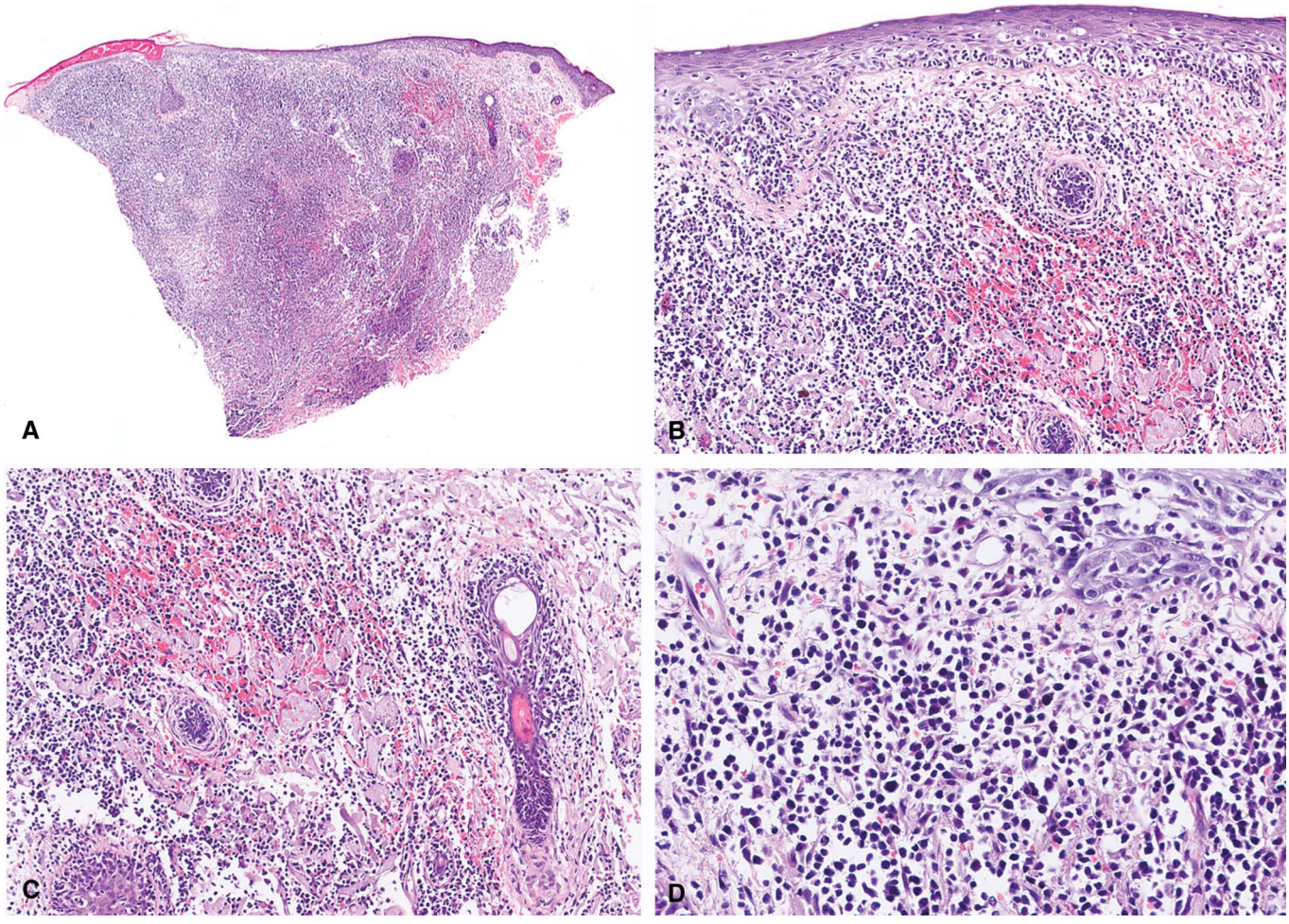

FIGURE 6. Case 2. A dense infiltrate in the dermis (A) with marked epidermotropism (B) and folliculotropism (C). The infiltrate is composed of small lymphocytes with hyperchromatic nuclei and halo (D).

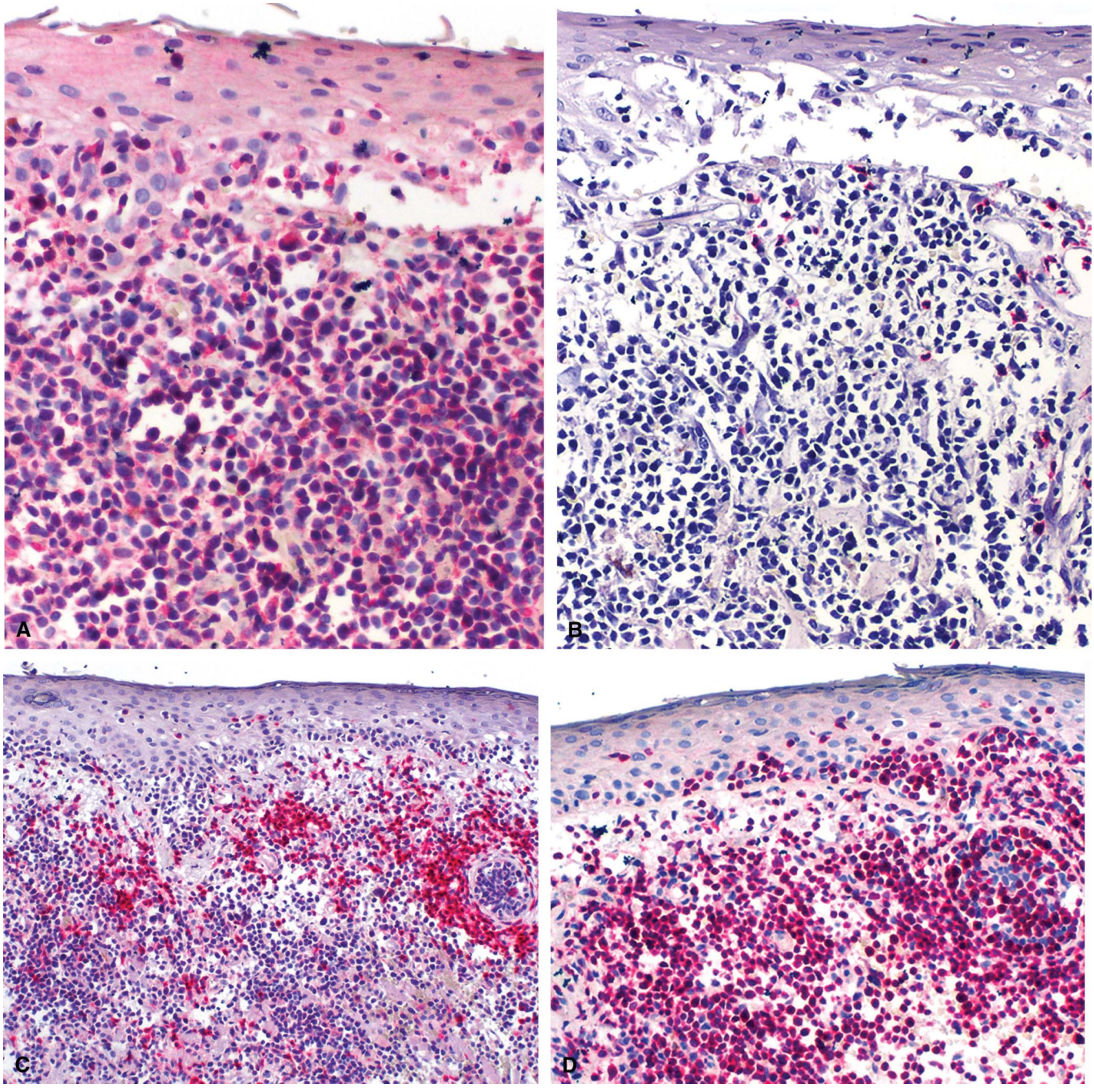

FIGURE 7. Case 2. Immunohistochemical staining for TCRγ (A), beta F1 (B), CD2 (C), and CD3 (D).

LyP type D, as with other LyP types, is characterized by papulonodular lesions with a typical waxing and waning course and spontaneous regression, whereas in our patients, no such clinical presentation was seen.[18–21] Our second case showed some features suggestive of folliculotropic MF. The absence of the subcutis in the biopsy specimen is a diagnostic limitation because CGD-TCL more often involves the subcutis than does folliculotropic MF. From the clinical standpoint, erosions are typical features of CGD-TCL. However, the good response to therapy with complete remission lasting 9 months would be unusual for CGD-TCL and would favor the diagnosis of MF. Based on the clinical presentation and the expression of TCRγ, however, this case may represent an unusual indolent epidermotropic and folliculotropic form of CGD-TCL.

The constellation in the presented cases exemplifies a diagnostic dilemma in CTCL. Expression of a γ/δ+ phenotype is an essential diagnostic criterion for CGD-TCL, but other forms of CTCL with their classic clinical presentation rarely can display γ/δ+ phenotype. Because of overlapping histological features with other CTCL, delineation from authentic

CGD-TCL on histopathological grounds alone is difficult and perhaps remains often arbitrary. Such cases raise the question, whether the demonstration of a γ/δ+ phenotype can be used as a necessary and sufficient criterion to classify the lymphomas as CGD-TCL with an unusually indolent course or whether the indolent course should be used as a decisive argument to classify them as MF with a γ/δ+ phenotype. The answer to this dilemma has not only an impact on the terminology and classification but also more importantly on the therapeutic approach. Because CGD-TCL is considered as an aggressive lymphoma with a poor prognosis, the diagnosis of this lymphoma usually implies the need for an aggressive therapeutic approach with multiagent chemotherapy, eventually in combination with alemtuzumab and followed by stem cell transplantation.[22] In contrast, phototherapy (psoralen-UV-A or UV-B narrowband) combined with topical corticosteroids or retinoids are the first-line strategy for MF in patch/plaque stage.[23,24] The situation becomes even more complex by the increasing insight into the wide prognostic spectrum even within the individual CTCL entities. For example, extranodal natural killer/T-cell lymphoma, nasal type, usually shows an aggressive course similar to CGD-TCL. However, cases with a chronic indolent course have recently been reported, challenging the concept that this lymphoma shows always an aggressive course and poor prognosis.[25] In analogy, one could argue that our cases represent an epidermotropic and folliculotropic subtype of CGD-TCL characterized by an indolent course and not requiring aggressive therapy. Recently, a case of a 57-year-old woman with a 3-year history of an indolent CGD-TCL was reported by Endly et al.[10] This CGD-TCL presented with nodules on the leg and predominantly subcutaneous γ/δ clonal T-cell infiltrates that rapidly improved within months of starting systemic corticosteroids.[10] Response of CGD-TCL with epidermotropic, dermal, and subcutaneous infiltrates to radiotherapy, retinoid, and UV-B narrowband was observed in a 62-year-old woman.[26] No matter what name is attached to similar cases, it will be important to identify prognostic and therapeutic markers for these rare CTCL.

A high number of PD-1–positive lymphocytes were found in case 1. The latter marker labels follicular helper T cells, which are normally present in germinal centers and possess helper function for B cells.[27] It also stains activated T cells and has been found in different forms of CTCL including MF and Sézary syndrome at variable degree range from 9% to 80% of cases harboring PD-1–positive T cells.[28,29] PD-1 is of interest because it may serve as a therapeutic marker.[30]

In conclusion, these 2 cases confirm the previous observation that a γ/δ phenotype in CTCL per se does not confer a worse prognosis in all cases. More studies and observations are warranted to shed light on the correct classifications of such cases to establish whether they represent a variant of MF or a more indolent form of epidermotropic or folliculotropic CGD-TCL for which less aggressive treatment may be effective.[10,26,31,32]

REFERENCES

1. Brenner MB, McLean J, Dialynas DP, et al. Identification of a putative second T-cell receptor. *Nature*. 1986;322:145–149.
2. Hocker TL, Wada DA, El-Azhary R, et al. Expression of T-cell receptor-gammadelta in normal human skin, inflammatory dermatoses and mycosis fungoides. *J Cutan Pathol.* 2012;39:419–424.
3. Toro JR, Liewehr DJ, Pabby N, et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood*. 2003;101:3407–3412.
4. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768–3785.
5. Burg G, Kempf W, Cozzio A, et al. WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. *J Cutan Pathol.* 2005;32:647–674.
6. Gaulard P, Berti E, Willemze R, et al. Primary cutaneous peripheral T-cell lymphomas, rare subtypes. In: Swerdlow S, Campo E, Harris NL, et al, eds. *WHO Classification of Tumors of the Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2008:302–305.
7. Roullet M, Gheith SM, Mauger J, et al. Percentage of {gamma}{delta} T cells in panniculitis by paraffin immunohistochemical analysis. *Am J Clin Pathol.* 2009;131:820–826.
8. Guitart J, Weisenburger DD, Subtil A, et al. Cutaneous gammadelta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. *Am J Surg Pathol.* 2012;36:1656–1665.
9. Rodriguez-Pinilla SM, Ortiz-Romero PL, Monsalvez V, et al. TCR-gamma expression in primary cutaneous T-cell lymphomas. *Am J Surg Pathol.* 2013;37:375–384.
10. Endly DC, Weenig RH, Peters MS, et al. Indolent course of cutaneous gamma-delta T-cell lymphoma. *J Cutan Pathol.* 2013;40:896–902.
11. van Dongen JJ, Langerak AW, Bruggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. *Leukemia.* 2003;17:2257–2317.
12. Munn SE, McGregor JM, Jones A, et al. Clinical and pathological heterogeneity in cutaneous gamma-delta T-cell lymphoma: a report of three cases and a review of the literature. *Br J Dermatol.* 1996;135:976–981.
13. Barzilai A, Goldberg I, Shibi R, et al. Mycosis fungoides expressing gamma/delta T-cell receptors. *J Am Acad Dermatol.* 1996;34:301–302.
14. Hodak E, David M, Maron L, et al. CD4/CD8 double-negative epidermotropic cutaneous T-cell lymphoma: an immunohistochemical variant of mycosis fungoides. *J Am Acad Dermatol.* 2006;55:276–284.
15. Kazakov DV, Burg G, Kempf W. Clinicopathological spectrum of mycosis fungoides. *J Eur Acad Dermatol Venereol.* 2004;18:397–415.
16. Yi L, Qun S, Wenjie Z, et al. The presenting manifestations of subcutaneous panniculitis-like T-cell lymphoma and T-cell lymphoma and cutaneous gammadelta T-cell lymphoma may mimic those of rheumatic diseases: a report of 11 cases. *Clin Rheumatol.* 2013;32:1169–1175.
17. Saggini A, Gulia A, Argenyi Z, et al. A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Description of 9 cases. *Am J Surg Pathol.* 2010;34:1168–1175.
18. El Shabrawi-Caelen L, Kerl H, Cerroni L. Lymphomatoid papulosis: reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. *Arch Dermatol.* 2004;140:441–447.
19. Kempf W, Kazakov DV, Baumgartner HP, et al. Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings. *J Am Acad Dermatol.* 2013;68:809–811.
20. Requena L, Sanchez M, Coca S, et al. Follicular lymphomatoid papulosis. *Am J Dermatopathol.* 1990;12:67–75.
21. Kempf W, Kazakov DV, Scharer L, et al. Angioinvasive lymphomatoid papulosis: a new variant simulating aggressive lymphomas. *Am J Surg Pathol.* 2013;37:1–13.
22. Koch R, Jaffe ES, Mensing C, et al. Cutaneous gamma/delta T-cell lymphoma. *J Dtsch Dermatol Ges.* 2009;7:1065–1067.
23. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer.* 2006;42:1014–1030.
24. Stadler R, Assaf C, Klemke CD, et al. Brief S2k guidelines—cutaneous lymphomas. *J Dtsch Dermatol Ges.* 2013;11(suppl 3):19–28, 20–30.

25. Zuriel D, Fink-Puches R, Cerroni L. A case of primary cutaneous extranodal natural killer/t-cell lymphoma, nasal type, with a 22-year indolent clinical course. *Am J Dermatopathol.* 2012;34:194–197.
26. Nakashima H, Sugaya M, Minatani Y, et al. Cutaneous gamma/delta T-cell lymphoma treated with retinoid and narrowband ultraviolet B. *Clin Exp Dermatol.* 2009;34:e345–e346.
27. Riley JL. PD-1 signaling in primary T cells. *Immunol Rev.* 2009;229:114–125.
28. Roncador G, Garcia Verdes-Montenegro JF, Tedoldi S, et al. Expression of two markers of germinal center T cells (SAP and PD-1) in angioimmunoblastic T-cell lymphoma. *Haematologica.* 2007;92: 1059–1066.
29. Wada DA, Wilcox RA, Harrington SM, et al. Programmed death 1 is expressed in cutaneous infiltrates of mycosis fungoides and Sezary syndrome. *Am J Hematol.* 2011;86:325–327.
30. Kempf W, Kazakov DV, Cipolat C, et al. In response. *Am J Dermatopathol.* 2013;35:691.
31. Caudron A, Bouaziz JD, Battistella M, et al. Two atypical cases of cutaneous gamma/delta T-cell lymphomas. *Dermatology*. 2011;222:297–303.
32. Fujii M, Uehara J, Honma M, et al. Primary cutaneous gammadelta-T-cell lymphoma treated with low-dose methotrexate and narrowband ultraviolet B irradiation: report of a case with testicular involvement. *J Dermatol.* 2011;38:368–372.